Anesthesiology 2006; 105:14–8

Intraoperative Tidal Volume as a Risk Factor for Respiratory Failure after Pneumonectomy

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Background: **Respiratory failure is a leading cause of postoperative morbidity and mortality in patients undergoing pneumonectomy. The authors hypothesized that intraoperative mechanical ventilation with large tidal volumes (V_Ts) would be associated with increased risk of postpneumonectomy respiratory failure.**

Methods: **Patients undergoing elective pneumonectomy at the authors' institution from January 1999 to January 2003 were studied. The authors collected data on demographics, relevant comorbidities, neoadjuvant therapy, pulmonary function tests, site and type of operation, duration of surgery, intraoperative ventilator settings, and intraoperative fluid administration. The primary outcome measure was postoperative respiratory failure, defined as the need for continuation of mechanical ventilation for greater than 48 h postoperatively or the need for reinstitution of mechanical ventilation after extubation.**

Results: **Of 170 pneumonectomy patients who met inclusion criteria, 30 (18%) developed postoperative respiratory failure. Causes of postoperative respiratory failure were acute lung injury in 50% (n = 15), cardiogenic pulmonary edema in 17% (n = 5), pneumonia in 23% (n = 7), bronchopleural fistula in 7% (n = 2), and pulmonary thromboembolism in 3% (n = 1). Patients who developed respiratory failure were ventilated with larger intraoperative V_T than those who did not (median, 8.3 *vs.* 6.7 ml/kg predicted body weight; $P < 0.001$). In a multivariate regression analysis, larger intraoperative V_T (odds ratio, 1.56 for each ml/kg increase; 95% confidence interval, 1.12–2.23) was associated with development of postoperative respiratory failure. The interaction between larger V_T and fluid administration was also statistically significant (odds ratio, 1.36; 95% confidence interval, 1.05–1.97).**

Conclusion: **Mechanical ventilation with large intraoperative V_T is associated with increased risk of postpneumonectomy respiratory failure.**

PNEUMONECTOMY is a high-risk surgical procedure that predisposes patients to postoperative respiratory failure and other pulmonary complications.[1–7] Several intraoperative risk factors for respiratory failure have been identified, including excessive perioperative fluid administration,[8] duration of operation,[9] extent of lung resection,[5,9] right-sided pneumonectomy,[10] and high intraoperative airway pressures.[11,12]

Mechanical ventilation of patients undergoing pneumonectomy is often accompanied by high intraoperative airway pressures. Potential causes of high airway pressures include a decrease in pulmonary compliance (*e.g.*, due to a decrease in the number of recruitable alveoli), an increase in pulmonary or airway resistance (*e.g.*, due to bronchospasm), and the use of large tidal volume (V_T). Alveolar overdistension associated with the use of large V_T may lead to alveolar stretch injury and the development of permeability pulmonary edema (ventilator-induced lung injury [VILI]).[11–19] Several recent reports have suggested that VILI can not only worsen preexisting acute lung injury (ALI) but can also initiate such injury in a previously normal lung.[15,17,20–23] Surgery that otherwise may be well tolerated can culminate in inflammatory injury when paired with another noxious influence such as VILI (multiple hit hypothesis).

Although mechanical ventilation with large V_T is the main risk factor for VILI,[21,24] no study has evaluated intraoperative V_T as a potential risk factor for postoperative complications. In this study, we sought to determine the incidence of and risk factors associated with postoperative respiratory failure in a cohort of patients undergoing pneumonectomy. We hypothesized that mechanical ventilation with large V_T during anesthesia would be associated with an increased incidence of postpneumonectomy respiratory failure.

This article is accompanied by an Editorial View. Please see: Slinger PD: Postpneumonectomy pulmonary edema: Good news, bad news. ANESTHESIOLOGY 2006; 105:2–5.

Materials and Methods

The study was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota). Only medical record data with patient written consent of research authorization was used in the study. From the institutional surgical database, we identified and reviewed the charts of consecutive patients who had undergone elective pneumonectomy at the Mayo Clinic in Rochester, Minnesota, between January 1, 1999, and January 1, 2003. Patients who had previously denied research authorization, those who were mechanically ventilated (invasively or noninvasively) in the preoperative period, and those who had undergone urgent or posttraumatic pneumonectomy were excluded from the study.

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Received from the Mayo Clinic College of Medicine, Rochester, Minnesota. Submitted for publication November 11, 2005. Accepted for publication February 23, 2006. Supported in part by a grant from the Mayo Foundation, Rochester, Minnesota (Dr. Fernández-Pérez and Dr. Brown) and grant No. K23 HL78743-01A1 from the National Institutes of Health, National Heart, Lung and Blood Institute, Bethesda, Maryland (Dr. Gajic). An abstract of this study was presented at the American College of Chest Physicians Annual Conference, Montréal, Québec, Canada, October 29–November 3, 2005.

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The primary endpoint of the study was development of postoperative respiratory failure, defined as the need for continuation of mechanical ventilation for greater than 48 h after surgery[25,26] or reinstitution of mechanical ventilation (invasive or noninvasive) at any time during the postoperative period. Patients requiring reintubation or mechanical ventilation for reoperation, elective procedures, or any complication other than respiratory failure due to a primary pulmonary process were excluded.

Secondary outcomes included postoperative pulmonary complications occurring within 60 days of thoracotomy, including ALI,[27] pneumonia,[28] pulmonary thromboembolism confirmed by contrast-enhanced chest computed tomography, cardiogenic pulmonary edema (distinct from ALI because of clinical evidence of left atrial hypertension), and bronchopleural fistula.[4]

The following data were abstracted from the medical records: age, sex, height, weight, body mass index, smoking and alcohol history, preoperative comorbidities (diabetes mellitus, hypertension, renal insufficiency, coronary artery disease, congestive heart failure), preoperative pulmonary function tests, the American Society of Anesthesiologists class, and the presence of neoadjuvant treatment (chemotherapy and/or radiation). Intraoperatively, side (left *vs.* right) and duration of surgery, total fluid infusion, and the largest V_T documented during anesthesia were recorded. Adjusted V_T was calculated according to lung size based on the predicted body weight[24] and forced vital capacity.

To minimize potential bias, one abstractor reviewed the primary outcome measure and the exposure to intraoperative variables in two separately occasions and collected the information in different secured databases. The investigators involved in the data analysis were blind to the intraoperative data until the completion of the study. To assess the reliability for the screening procedure for ascertainment of postoperative respiratory failure, we randomly selected 20 patients among those without respiratory failure and verified whether postoperative respiratory failure criteria were present in the body of the record. None of them had any respiratory failure mentioned in the body of the record.

Statistical Analysis

To compare patients who did and did not develop postoperative respiratory failure, we used the Wilcoxon or Student *t* test for continuous variables and chi-square or Fisher exact for categorical variables. To determine independently associated risk factors, we created a stepwise multivariate logistic regression model with postoperative respiratory failure as the dependent variable. Risk factors for postoperative respiratory failure were considered for the multivariable logistic regression model if they (1) were statistically significant in the bivariate analyses ($P < 0.05$), (2) had high odds ratios (≥ 1.5) for categorical variables or for the range of continuous variables, (3) were biologically plausible, and (4) had 20% or less missing data. For variables that were significant, two-way interactions were considered. When interactions were included in the model, the main effects from the interaction were included as covariates. The variables were treated as continuous or categorical according to their data distribution, the goodness of fit of the overall model, and the presence or absence of a clinically meaningful threshold value. All statistical tests were two sided. JMP statistical software (JMP, version 5.1; SAS Institute Inc., Cary, NC) was used for data analyses.

Results

From a total of 176 patients who had undergone elective pneumonectomy, 6 patients were excluded (4 subjects did not authorize the use of their medical record for research, and 2 patients were mechanically ventilated before surgery).

Therefore, there were 170 eligible study patients who underwent pneumonectomy, and 30 (18%) developed postoperative respiratory failure. After the operation, 25 patients were reintubated, 3 patients required continuation of mechanical ventilation for more than 48 h postoperatively, and 2 patients were treated with noninvasive positive-pressure ventilation. Causes of postoperative respiratory failure were ALI in 50% (n = 15), cardiogenic pulmonary edema in 17% (n = 5), pneumonia in 23% (n = 7), bronchopleural fistula in 7% (n = 2), and pulmonary thromboembolism in 3% (n = 1). Table 1 demonstrates the clinical characteristics of patients who did and did not develop postoperative respiratory failure after pneumonectomy. There were no significant differences in age, sex, comorbid conditions (coronary artery disease, diabetes, hypertension, congestive heart failure), creatinine, baseline pulmonary function tests, smoking and alcohol history, American Society of Anesthesiologists class, the presence of neoadjuvant treatment, side of pneumonectomy, and duration of anesthesia between patients who did and did not develop respiratory failure. However, patients who developed respiratory failure were ventilated with larger intraoperative V_T than those who did not (median, 8.3 *vs.* 6.7 ml/kg predicted body weight; $P < 0.001$; fig. 1) and received larger intraoperative fluid volumes (median, 2.2 *vs.* 1.3 l, respectively; $P = 0.001$). In a multivariate logistic regression analysis, larger intraoperative V_T was associated with the development of postoperative respiratory failure (table 2). The interaction between larger V_T and fluid administration was also statistically significant (table 2). Patients who developed postoperative respiratory failure had a higher 60-day mortality (23% *vs.* 4%; $P = 0.02$) and longer hospital durations of stay (median, 22 *vs.* 6 days; $P = 0.001$). Six of the 15 patients developing postoperative ALI died (40%), compared with only 1 of the 15 patients with non-ALI postoperative respiratory failure (6.6%). No signif-

Table 1. Characteristics of Patients Who Did and Did Not Develop Respiratory Failure after Pneumonectomy

Variable	Patients with Respiratory Failure (n = 30)	Patients without Respiratory Failure (n = 140)	*P* Value
Female sex	16 (53%)	47 (34%)	0.062
Age, yr	61 (55–70)	63 (54–70)	0.285
Comorbid conditions			
Coronary artery disease	6 (20%)	16 (11%)	0.241
Hypertension	6 (20%)	29 (20%)	0.937
Diabetes	3 (10%)	10 (7%)	0.451
Congestive heart failure	1 (3%)	5 (4%)	0.324
Serum creatinine, mg/dl	0.9 (0.8–1)	1 (0.9–1.2)	0.061
PFTs, % predicted value			
FEV_1	67 (59–77)	71 (56–83)	0.265
FEV_1/FVC	69 (65–80)	72 (67–79)	0.884
FVC	72 (62–80)	77 (66–90)	0.068
DLCO	72 (61–86)	81 (68–97)	0.081
Smoking history	23 (76%)	88 (62%)	0.284
Alcohol history	9 (30%)	45 (32%)	0.831
Previous chemotherapy	8 (27%)	36 (26%)	1
Previous radiation therapy	3 (10%)	12 (9%)	0.877
ASA class			0.175
I, II	3 (10%)	30 (21%)	
III, IV	27 (90%)	110 (79%)	
Pneumonectomy			0.485
Right sided	17 (57%)	70 (50%)	
Left sided	13 (43%)	70 (50%)	
Anesthesia			
Duration, min	352 (244–453)	290 (240–374)	0.131
Fluid input, l	2.2 (1.4–3.7)	1.3 (0.9–2.7)	0.001
Tidal volume			
ml/kg PBW	8.3 (7.6–9.4)	6.7 (6.1–7.9)	< 0.001
Proportion of FVC	0.19 (0.16–0.27)	0.15 (0.12–0.18)	0.008

Data are represented as median (interquartile range) and number (percentage).

ASA = American Society of Anesthesiologists; DLCO = diffuse capacity of lungs for carbon monoxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; PBW = predicted body weight; PFT = pulmonary function test (preoperative).

icant differences were observed in the hospital duration of stay between patients who developed ALI and those with other causes of postoperative respiratory failure (median, 27 *vs.* 16 days; $P = 0.204$).

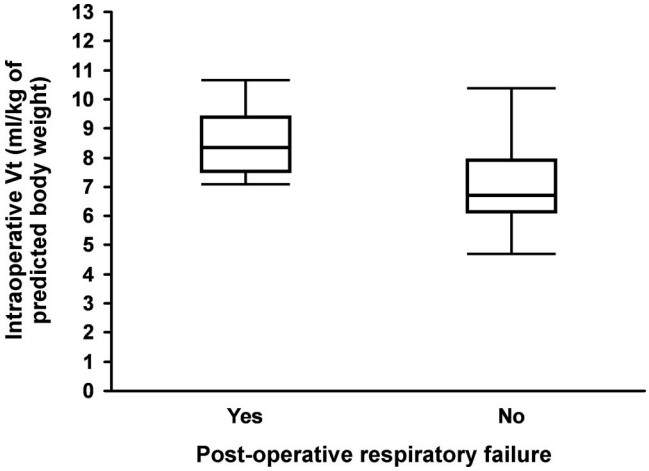

Fig. 1. Median (*horizontal line*), 25th and 75th percentiles (*box*), and range (*whiskers*) of intraoperative tidal volume (V_T) in patients who did and did not develop postpneumonectomy respiratory failure.

Discussion

In this historical cohort study of patients undergoing pneumonectomy at a teaching institution, intraoperative large V_T and larger amount of fluid administration were associated with the development of postoperative respiratory failure. Patients who developed postoperative respiratory failure had a longer hospital duration of stay and higher mortality.

Our data suggest that mechanical ventilation with large intraoperative V_T is an important risk factor for develop-

Table 2. Risk Factors Associated with Development of Postoperative Respiratory Failure: Multivariate Logistic Regression Analysis

	Odds Ratio	95% CI Lower	95% CI Upper	*P* Value
Intraoperative V_T	1.56*	1.12	2.23	0.009
Preoperative FVC	0.98†	0.96	1.01	0.206
Fluid	1.34‡	0.83	2.09	0.201
Intraoperative V_T × fluid	1.36§	1.05	1.97	0.005

* Per each ml/kg predicted body weight. † For each percent decline in forced vital capacity. ‡ Per liter of fluid infused intraoperatively. § Interaction (evaluated by adding the cross-product term in the logistic regression model).

CI = confidence interval; FVC = forced vital capacity; V_T = tidal volume.

ment of postoperative respiratory failure in patients undergoing pneumonectomy. The adverse effects of mechanical ventilation with large V_T and high airway pressure are well described in patients with ALI who are mechanically ventilated in the intensive care unit.[24] In this group of patients, low V_T ventilation is associated with a more rapid attenuation of the inflammatory response.[29] Similarly, in a recent prospective randomized study, the use of smaller V_T in patients undergoing thoracic surgery resulted in a significant decrease of alveolar inflammatory cytokines.[30]

Our study suggests that even brief exposure to adverse ventilator settings during surgery may result in clinically significant VILI and adverse postoperative outcome. This may come as no surprise given the experimental evidence that even brief periods of mechanical ventilation with large V_T may result in VILI. VILI can be demonstrated after only 20 min of large V_T ventilation in small animals[21] and after 2 h of large V_T ventilation in larger mammals.[31,32] Two previous studies demonstrated that high intraoperative airway pressures were associated with development of ALI after lung resection.[11,12] Van der Werf *et al.*[12] studied 190 patients who underwent lung resection and found that peak inspiratory pressures in excess of 40 cm H_2O were associated with the development of postpneumonectomy pulmonary edema (relative risk, 3.0; 95% confidence interval, 1.2–7.3). In a recent cohort study of 879 patients undergoing pneumonectomy for lung cancer, the "ventilatory hyperpressure index" (product of duration of one-lung ventilation and inspiratory plateau pressure exceeding 10 cm H_2O) was associated with the development of ALI in the postoperative period (odds ratio, 3.53; 95% confidence interval, 1.71–8.45).[11]

The incidence rate of postoperative respiratory failure from this study is in the range of those published from single-institution retrospective series.[1,2,7,33] Also, the 60-day postoperative mortality rate was similar to those previously reported.[2,4,34]

Although some investigators have not shown an association between larger intraoperative fluid administration and respiratory failure,[35] the current study is in agreement with other reports suggesting that excessive intraoperative fluid administration may be a contributing factor in the development of postpneumonectomy respiratory failure.[8,11] Recent studies in nonthoracic surgery patients also support these findings.[36,37] The significant interaction between large V_T and fluid administration is perhaps the most interesting finding in our study. Two mechanisms may explain this association. First, greater fluid administration may have been the consequence of large V_T ventilation. Large V_Ts predispose to air trapping and to paradoxic pulse in the operating room and may also increase the right ventricular afterload. Therefore, the resulting hypotension forces the anesthesiologist to administer fluids. Moreover, the interaction between V_T and lung hemodynamics can also affect the clinical manifestations of VILI.[38]

There are several limitations of our study design. The observational nature of the study does not allow estimation of the cause-and-effect relation between the risk factors and outcome because unmeasured confounding factors may not have been accounted for. For example, larger intraoperative V_Ts and higher airway pressures may be a marker for lung disease and hypoxemia and not causative of lung injury and/or postoperative respiratory failure. However, the current practice of setting the ventilator at 10 ml/kg per actual body weight may create a setting for "natural experiment" where women, shorter and obese patients, and those with preexisting restrictive lung disease are exposed to much higher V_T per lung size. Indeed, women in our study were ventilated with higher intraoperative V_T (ml/kg of predicted body weight) than men (8.3 *vs.* 6.3; $P = 0.001$) and tended to develop postoperative respiratory failure more often (16 [25%] *vs.* 14 [13%] of total cases of pneumonectomies; $P = 0.062$).

Importantly, our analysis was based on a single largest V_T charted during anesthesia. We were unable to precisely determine the V_Ts and airway pressures (positive end-inspiratory pressure, peak and plateau airway pressure) used during the period of one-lung ventilation because of incomplete or missing data in the medical records (> 20% missing data). Although a positive end-inspiratory pressure level of zero was used as a default setting during anesthesia at our institution during the study period, the changes in positive end-inspiratory pressure as a response to intraoperative hypoxemia were not consistently charted at the time of the study. Therefore, we were not able to evaluate the cumulative exposure to potentially harmful ventilator settings.

In conclusion, the association between large V_T and larger fluid administration with the development of postoperative respiratory failure is the most interesting finding of this study. It raises important implications with regard to the etiology of postoperative respiratory failure and ALI, and possible prevention strategies. Randomized clinical trials are needed to determine optimal intraoperative ventilator settings and fluid management in patients undergoing high-risk operations such as pneumonectomy. While awaiting the results of such studies, anesthesiologists should be aware of the potential risks associated with large V_T ventilation.

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